REMARKS

New claim 21 has been introduced. Support for claim 21 can be found on page 6, line 7 of the Specification as originally filed. No new matter has been introduced. In view of the following remarks, reconsideration of the present patent application is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briggner et al. (US Patent 5,874,063) in view of Gennaro et al. (Remington's Pharmaceutical Sciences, 1990, 18th edition, page 1699-1701, and 1706-1707), O'Connor (Pulmonary & Therapeutics, 1988; 11:397-399), Sequeira et al. (US Patent 5,837,699), and Sequeira '393 (WO95/20393). Applicants respectfully traverse.

Briggner et al. describes a process for preparing finely divided particles of a pharmaceutical substance with specified heat-emitting characteristics. It is indicated in claim 1 that the pharmaceutical substance may be a mixture of inhalation drugs. This corresponds to the statement in column 2, lines 32-34, that the pharmaceutical substance may be mixture of two or more drugs. However, the only specific mixture of drugs disclosed is a mixture of formoterol fumarate dihydrate and budesonide. This reflects the fact that the inventors of Briggner et al. were concerned with teaching a process for preparing improved particles of known pharmaceutical substances and not with making suggestions for mixing together drugs which had not previously been mixed together. Mixtures of formoterol fumarate dihydrate and budesonide had previously been disclosed in WO93/11773, published 24.6.93. There is no suggestion that other mixtures of formoterol and steroids could be used; the Examiner recognizes this in stating, in the first full paragraph on page 3 of the Office Action, that Briggner et al. does not teach the use of mometasone in the inhalation formulation. There is nothing in Briggner et al. to motivate those of ordinary skill in the art, seeking a novel pharmaceutical substance with improved therapeutic properties, to combine formoterol with mometasone. Those of ordinary skill in the art would clearly have read Briggner et al. as teaching a method of improving the particulate form of known pharmaceutical substances, including known mixtures of drugs.

Gennaro et al. does not make up for the deficiencies of Briggner et al. It teaches steroids in dispersion or suspension as suggested by the Examiner, but this document is concerned with vehicles for, and formulation techniques for, the preparation of aerosols from known materials, including known pharmaceutical substances. There is nothing in this document teaching those of ordinary skill in the art anything which would lead them towards an aerosol comprising a mixture of formoterol and mometasone.

O'Connor does not make up for the deficiencies of Briggner et al. O'Connor is cited as teaching that employment of the combination of β-agonist and steroid is more effective than either agent alone in the management of asthma. However, it is clear that O'Connor is not enunciating a general teaching. The passage cited in support of this alleged teaching is summarising the results of studies with 3 particular combinations of a specific β-agonist and a specific steroid, i.e. salmeterol-beclamethasone dipropionate, salmeterol-fluticasone and formoterol-budesonide. The quoted teaching of O'Connor, page 398, col 2, second paragraph, is a teaching that the results of combining formoterol and budesonide are additive rather than synergistic.

With regard to Sequeira '393, the Examiner points out that it discloses that mometasone can be used as adjuvant therapy with bronchodilators in a therapeutic composition. However, it is significant that although formoterol had been known for more than 20 years before the priority date of Sequeira '393, and was already in clinical use at that priority date, the only bronchodilators suggested for adjuvant therapy are albuterol and theophylline. Hence, this disclosure effectively teaches away from the use of a combination of formoterol and mometasone and so has a demotivating, rather than a motivating, effect when considered together with the other cited references.

With reference to Sequeira et al, the Examiner suggests that one of ordinary skill in the art would have been motivated to employ 25 to 800μg of mometasone and 3 to 36μg of formoterol into an aerosol dosage form because both 25 to 800μg of mometasone and 12μg of formoterol were known to be useful in treating asthma, and combining two agents known to be useful for treating asthma individually into a single composition useful for the same purpose is prima facie obvious. However, it is respectfully submitted that the evidence of the cited prior art and other prior art points to an opposite conclusion. As the Examiner points out, the use of formoterol with a steroid in the treatment of asthma had been disclosed in the prior art (O'Connor), that steroid being budesonide, but, as the teaching of O'Connor cited by the Examiner on page 3 of the Action shows, the results were additive. Hence there would have been no motivation to combine formoterol and mometasone into a single composition.

The Examiner then states that it is known that combining a long-acting, inhaled β2-agonist with an inhaled glucocorticoid led to a greater improvement in the control of symptoms and in lung function than doubling the dose of the glucocorticoid. This statement refers to a passage in Pauwels et al. (New England Journal of Medicine, 1997; 337(20): 1405-1411) which was cited against parent case Serial No. 09/942,805 but is not cited in the present Action, and relates to combinations of salmeterol with a steroid. Salmeterol and formoterol differ

considerably in chemical structure and pharmacological profile; for example, formoterol is a full β2-agonist whereas salmeterol is a partial β2-agonist, which partial agonism is understood to be the basis of the long duration of action of salmeterol. It is thus not scientifically sound to predict that formoterol would give similar results to salmeterol in combination with a steroid.

The Applicants respectfully refute the suggestion that because the use of formoterol and mometasone individually in the treatment of asthma had previously been described, combining them in the treatment of asthma is prima facie obvious. Apart from the de-motivating effect of the prior art mentioned above, the therapeutic effects of combining two drugs depend on the interactions between the drugs, which are not predictable from the effects of the two drugs when used alone. Prior to the instant invention, there was nothing to indicate the likely interactions of formoterol and mometasone.

The physical and pharmacological effects of combining formoterol and mometasone into a single composition for inhalation were inherently unpredictable.
The compatibility of formoterol and mometasone furoate was completely unpredictable to those of ordinary skill in the art. It was impossible to predict interactions between formoterol and mometasone furoate, taking into account both pharmacodynamic and pharmacokinetic effects such as absorption, biotransformation and elimination. It was also impossible to predict the stability of a mixture of formoterol and mometasone furoate, whether in the absence of other components or in the presence of other components such as the solvents used as propellants in aerosol compositions. A stable formulation is an essential requirement for a useful pharmaceutical product.

Formoterol has proved a difficult substance to formulate into an inhalable composition delivering consistent doses of the drug which explains why, although it was known as a bronchodilator more than 25 years ago, it was not until 2001 that its use in treatment of asthma was approved by the FDA. Formoterol has a formamido group, which renders the molecule susceptible to chemical degradation when mixed with carriers such as lactose. The addition of a further component having potentially reactive moieties increases the complexity of possible degradation processes. There is nothing in the prior art which would have led those of ordinary skill in the art to believe that mixing formoterol with mometasone in the same composition would have resulted in a stable composition with advantageous pharmacological properties.

The claimed medicament has been shown to give unexpected advantageous properties compared with what would have been expected from the properties of formoterol and mometasone individually. The Declaration of Dr. Fromond submitted in response to the first

Office Action in Serial No. 09/942,805 shows a synergistic anti-inflammatory effect for a combination of particular doses of formoterol and mometasone.

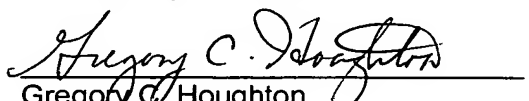
The Declaration of Dr. Trifilieff submitted herewith shows a synergistic effect for a combination of formoterol and mometasone over a different, much wider range of doses, with dose ratios of formoterol to mometasone ranging from 1:2 to 1:100. This Declaration relates to comparative tests in an animal model measuring bronchoconstriction following antigen challenge, the test results showing the comparative effects of formoterol, mometasone and combinations of formoterol and mometasone in reducing the bronchoconstriction induced by the antigen, i.e. the comparative effects in improving lung function. The results show a considerable synergistic effect for the combination of formoterol and mometasone, for all doses of formoterol and mometasone used.

Also, the Examiner suggests that the claims are not limited to the synergistic amount of formoterol and mometasone as supported by the animal data. The only meaningful way to correlate the synergistic amount of formoterol and mometasone between humans and the animal test data in the present application is clinically which, as the Examiner can well appreciate, is prohibitively expensive, time-consuming and quite restrictive. It would therefore be unreasonable to require that clinical trials are conducted to correlate any synergistic amount between human models and animal models. It is therefore Applicant's conviction that the unexpected results of the combination of formoterol and mometasone as described in the Declaration of Dr. Trifilieff and supported by the application supports the claims now pending.

Based on the foregoing, Applicants respectfully request that the 35 U.S.C. §103(a) rejection be reconsidered and withdrawn with respect to claims 1-20.

In view of the remarks and the amendments, further and favorable consideration of the present application and the allowance of all pending claims are respectfully requested. The Examiner is also invited to contact the undersigned should the Examiner believe that such contact would expedite prosecution of the present application.

Respectfully submitted,



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Date: 9/23/04

Case 4-30843D/HO 16

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
IAN FRANCIS HASSAN ET AL
APPLICATION NO: 10/718,316
FILED: November 20, 2003
FOR: COMBINATIONS OF FORMOTEROL AND MOMETASONE FUROATE FOR ASTHMA

Group Art Unit: 1617
Examiner: HUI, SAN MING R

DECLARATION UNDER RULE 132

I, Alexandre Trifilieff, a citizen of France, declare:

1. I am a graduate of the University of Provence, Marseille, France, where I was awarded the degree of Bachelor of Science in Biochemistry in 1989. I was awarded the degree of Master of Science in Pharmacology in 1990 and the degree of Doctor of Philosophy (PhD) in Pharmacology in 1993 by the University Louis Pasteur, Strasbourg, France, my thesis being entitled "Kinins airway receptors".

I was a Post-Doctoral Fellow at the University of Southampton, United Kingdom, from 1993 to 1995, specialising in cell culture and immunohistochemistry techniques on bronchial biopsies and cultured epithelial cells, particularly with respect to their application to the characterization of inflammatory cells and adhesion molecules in asthma. I was a Post-Doctoral Fellow in the Respiratory Disease Department of Ciba-Geigy AG, Basel, Switzerland, from 1995 to 1997, specialising in the development of *in vivo* murine models of asthma, immunohistochemistry and morphometric studies on lung tissues and cultured pulmonary cells, and primary culture of pulmonary smooth muscle and epithelial cells, particularly with respect to their application to the characterization of inflammatory reactions and the remodelling process in the airway.

Since June 1997, I have held the position of Biology Laboratory Head in the Horsham Research Centre of Novartis Pharmaceuticals UK Limited, and have been leader or co-leader of various pre-clinical programs, specialising in the development of *in vivo* models of lung inflammation.

I am the co-author of 34 scientific papers on inflammation and related pharmacology, particularly of the airways, which have been published in scientific journals of high standards, such as Journal of Immunology, European Journal of Pharmacology, British Journal of Pharmacology, Journal of Clinical Investigation and American Journal of Respiratory and Critical Care Medicine.

2. The following tests were carried out under my supervision:

The comparative effects of formoterol, mometasone furoate and a combination of formoterol and mometasone furoate on lung function following antigen challenge were studied in immunised 6 week- old female BALB/c mice obtained from Charles River (Margate, UK). All experiments conformed to the UK Animals (Scientific Procedures) Act 1986.

The mice were immunised intraperitoneally on day 0 and day 14 with 20μg of ovalbumin (grade V, Sigma, Poole, UK) in 0.1ml of alum (Serva, Heidelberg, Germany). On days 21, 22 and 23, the mice were exposed, for 20 minutes, to an aerosol of 1 % ovalbumin in phosphate buffered saline (PBS). On day 26, the baseline airway responsiveness of each animal was measured for 5 minutes using whole body plethysmography and enhanced pause (Penh) values determined following the procedure of E. Hamelmann et al, Am J Respir Crit Care, Vol. 156, pp. 766-775, 1997, and then, in a final antigen challenge, the mice were exposed, for 20 minutes, to an aerosol of 5% ovalbumin in PBS or PBS alone.

One hour after the last challenge, different groups of the ovalbumin-challenged mice were treated intranasally with solutions of 50μl PBS containing respectively 1) 2% N-methyl-pyrrolidone (Control), 2) formoterol fumarate dihydrate in 2% N-methylpyrrolidone, 3) mometasone furoate in 2% N-methylpyrrolidone, and 4) formoterol fumarate dihydrate and mometasone furoate in 2% N-methylpyrrolidone. The doses of formoterol fumarate dihydrate and mometasone furoate used in solutions 2), 3) and 4) are given under Results below. The doses of 15 microg/kg formoterol fumarate dihydrate alone and 300 microg/kg

mometasone furoate alone were used only in order to assist in the plotting of dose response curves. Four hours after the last antigen challenge, the airway responsiveness of each animal was measured again as previously for 5 minutes using whole body plethysmography and the Penh values determined. The ratio of the Penh value post antigen challenge to the baseline Penh value was recorded for each of the animals. The increases in Penh values after antigen challenge are a measure of the bronchoconstriction resulting from the challenge. Dose response curves were plotted for the Penh post antigen : baseline ratio.

3. The experimental data were analysed as follows :

The possible synergistic interaction between the two compounds was analyzed by the algebraic method developed by Berenbaum (M C Berenbaum, *Clinical and Experimental Immunology 28, 1-18* (1977). Based on experimental data, the following coefficient, the "Berenbaum coefficient", was calculated:

M/Me + F/Fe

where M and F are the doses of mometasone furoate and formoterol fumarate dihydrate respectively, given in combination, that achieve a given quantitative effect; and

Me and Fe are the doses of mometasone furoate and formoterol fumarate dihydrate respectively, given alone, that produce the same quantitative effect, i.e. ratio of Penh post antigen to Penh baseline (equi-effective dose, obtained by extrapolation of the Penh ratio dose response curve for each entity).

A coefficient of 1 indicates an additive effect, a coefficient of less than one a synergistic effect and a coefficient greater than 1 an antagonistic effect, between the two compounds.

Results were expressed as means ± standard error of the mean.

4. The results of the above tests and my conclusions therefrom are as follows:

Results

The determined Penh values for various doses of formoterol fumarate dihydrate, mometasone furoate and a combination of the two are given in the following table:

Penh values

			Formoterol (microg/kg)			
			0	1	5	15
Mometasone (microg/kg)	0	Baseline	163 ± 7	165 ± 8	161 ± 5	168 ± 9
		+4hrs	564 ± 77	545 ± 59	388 ± 63	302 ± 47
	10	Baseline	197 ± 4	180 ± 4	169 ± 8	
		+4hrs	621 ± 75	452 ± 50	307 ± 27	
	100	Baseline	157 ± 5	172 ± 8	172 ± 9	
		+4hrs	492 ± 84	304 ± 50	239 ± 37	
	300	Baseline	173 ± 7			
		+4hrs	406 ± 41			

The ratios of the Penh value post antigen challenge to the baseline Penh value for various doses of formoterol fumarate dihydrate, mometasone furoate and a combination of the two were as shown in the following table:

Ratios of the Penh value post antigen challenge to the baseline Penh value

		Formoterol (microg/kg)			
		0	1	5	15
Mometasone (microg/kg)	0	3.43	3.36	2.42	1.79
	10	3.15	2.5	1.84	
	100	3.11	1.77	1.41	
	300	2.57			

For the four combinations of formoterol and mometasone shown in the above table, the values of F, M, Fe and Me for calculation of the Berenbaum coefficient are shown in the following table together with the ratios of the measured Penh values, Fe and Me being obtained by extrapolation of the dose response curves for formoterol and mometasone respectively. The resulting Berenbaum coefficients for the combinations are also shown.

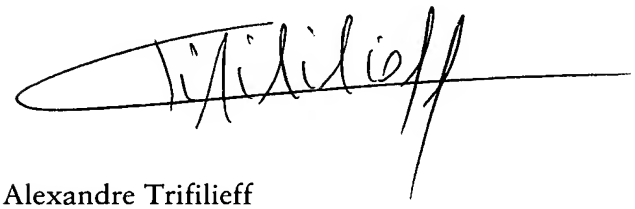
F (microg/kg)	M (microg/kg)	Penh ratio	Fe (microg/kg)	Me (microg/kg)	Berenbaum coefficient
1	10	2.5	4.9	366.6	0.23
5	10	1.84	11.5	736.6	0.45
1	100	1.77	11.8	738.7	0.22
5	100	1.41	23.8	987.8	0.31

Conclusions

The results show that the combination of formoterol fumarate dihydrate and mometasone furoate gives a considerable synergistic improvement in lung function compared with the sum of the effects of an equi-effective dose of formoterol fumarate dihydrate alone and an equi-effective dose of mometasone furoate alone, irrespective of the actual doses used. This synergistic effect has been clearly shown shown for a wide range of ratios of formoterol dose to mometasone dose, from 1:2 to 1:100.

4. I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signed this day of 16th of September 2004



Alexandre Trifilieff